B. REMARKS

Upon entry of the present amendment, claims 1 to 56 will be pending.

A. Regarding the Amendments

The specification has been amended such that the "Brief Description" of Figures 1A and 1B indicate that the number in parentheses on Replacement Figures 1A and 1B is the "SEQ ID NO:" In connection with this amendment, Replacement Figures 1A and 1B are submitted herewith, indicating the Sequence Identifies for the sequences shown in the Figures. A marked version of Figures 1A and 1B also is provided, with the newly inserted SEQ ID NOS: underlined. It is submitted that the amendments merely address a formality, and do not add new matter. As such, entry of the amendment and the Replacement Figures 1A and 1B is respectfully requested.

Pursuant to the restriction requirement, claims 57 to 74 are canceled herein with disclaimer, and without prejudice to Applicants' pursuing prosecution of subject matter encompassed within one or more of the claims in an application claiming the benefit of priority of the subject application.

Claims 1, 15, and 25 have been amended to more clearly indicate that a method of the invention generates a recombinant double stranded (ds) nucleic acid molecule that does not contain a nick at the position (ends) at which the two ds nucleotide sequences are joined. The amendment is supported, for example, at paragraph 36 (page 18), and paragraph 94 (pages 44-45) (see, also, Figure 1B), and, therefore, does not add new matter.

B. Regarding the Information Disclosure Statement

It is noted that references WO 97/48716 and WO 98/56943 listed in a Form 1449 submitted with an Information Disclosure Statement for the subject application were not initialed

by the Examiner as indicating that the references were submitted. For the Examiner's convenience, a copy of the Form 1449 is attached. Applicants respectfully request that the Examiner consider these two cited references, and indicate such consideration by initialing the Form 1449 and returning it to Applicants' representative with the next Communication for this case. If there is any reason the references cannot be considered, it is respectfully requested that the Examiner contact Applicants' undersigned representative.

C. Regarding the Restriction Requirement

The finality of the Restriction Requirement is acknowledged. The non-elected claims have been cancelled.

D. Objection to the Specification

It is noted in the Office Action that the Figures contain sequences that are subject to 37 C.F.R. § 1.821 et seq., but are not identified by Sequence Identifier. Replacement Figures 1A and 1B are submitted herewith, with the appropriate Sequence Identifier indicated in parentheses, and the Brief Description of Figures 1A and 1B has been amended to indicate that the numbers shown in parentheses are the Sequence Identifiers. It is noted that the sequences shown in Figures 1A and 1B were present in the Sequence Listing as originally filed with the subject application. In view of the amendment and Replacement Figures 1A and 1B, it is respectfully requested that this objection to the specification be withdrawn.

E. Prior Art Rejections

The rejection of claims 1 to 5, 8 to 10, 12 to 14, 25, 26, 28 to 31, 37 to 41, 44, 45, and 49 to 54 under 35 U.S.C. § 102(b) as allegedly anticipated by Shuman is respectfully traversed.

Shuman is cited as describing a method of generating a double stranded (ds) recombinant nucleic acid by contacting a first ds nucleotide sequence, a second ds nucleotide sequence, and a

topoisomerase such that the topoisomerase covalently link both strands of the first sequence to the second sequence. Shuman describes methods for linking duplex DNA molecules using topoisomerase. Referring to Figure 5, Shuman shows a first ds nucleotide sequence having a topoisomerase bound to each 3' terminus ("topoisomerase charged bivalent linker"), and a second ds nucleotide sequence comprising a linearized vector (Hind III cleaved pUC18). Upon contact of the first and second ds nucleotide sequences shown in Figure 5, the 3' termini of the first ds nucleotide sequence (shown with the "T" topoisomerase) will be covalently linked to the 5' termini of the second ds nucleotide sequence (see, also, col. 7, lines 13-27). As such, the first ds nucleotide sequence is linked to the vector in one strand at each end, but not in the second strand of each end.

The present claims require that the topoisomerase covalently link both strands of at least one end of the first ds nucleotide sequence to both strands of at least one end of the second ds nucleotide sequence to obtain a recombinant ds nucleic acid molecule that "does not contain a nick in either strand at the position where the ds nucleotide sequences are joined". As discussed in the Interview with the Examiner, the generation of a ds recombinant nucleic acid molecule according to a method of the invention is exemplified in Figure 1B. For illustrative purposes, the Examiner's attention was directed to the left ("first") end of the "first" ds nucleotide sequence shown in the top panel of Figure 1B, in which a topoisomerase is shown bound to the 3' terminus of the first end of the first ds nucleotide sequence; and was further directed to the right ("first") end of the "second" ds nucleotide sequence shown as "Element1" in the middle panel of Figure 1B, in which a topoisomerase is bound to the 3' terminus of the first end of the second ds nucleotide sequence. As shown in the third panel of Figure 1B, contact of the first end of the first ds nucleotide sequence and the first end of the second ds nucleotide sequence results in covalent linkage of both strands of the first ends, thereby generating a ds recombinant nucleic acid molecule that does not contain a nick at the joined "first ends".

For the above reasons, it is submitted that the claimed methods, which are directed to generating a ds recombinant nucleic acid molecule lacking a nick at the position at which two ds nucleotide sequences are joined, are novel over Shuman. Accordingly, it is respectfully requested that the rejection of the claims as anticipated by Shuman be removed.

The rejection of claims 32 to 34 and 36 under 35 U.S.C. § 103(a) as allegedly obvious over Shuman is respectfully traversed.

Shuman is applied for the reasons set forth above. It is acknowledged in the Office Action that Shuman does not teach using a third ds nucleotide sequence, but alleged that the skilled artisan would have been motivated to further bind a third ds nucleotide sequence to generate a desired construct. As discussed above, however, the claimed methods are distinguishable from Shuman in providing a method for covalently linking both strands of at least one end of the first ds nucleotide sequence to both strands of at least one end of the second ds nucleotide sequence to generate a ds recombinant nucleic acid molecule that has no nick at the position of the joined ends. As such, even if one of ordinary skill in the art, viewing Shuman, would have been motivated to link three ds nucleotide sequences, the artisan would not have obtained a ds recombinant nucleic acid molecule in which at least one end of a first ds nucleotide sequence is covalently linked to both strands of one end of a second ds nucleotide sequence, as required by the present methods. Accordingly, it is submitted that the claimed invention would not have been obvious in view of Shuman and, therefore, respectfully requested that the rejection of claims 32 to 34 and 36 as obvious over Shuman be removed.

The rejection of claims 6, 7, 11, 15 to 24, 27 and 35 under 35 U.S.C. § 103(a) as allegedly obvious in view of Shuman in view of Yarovinsky is respectfully traversed.

Shuman is applied as discussed above. Yarovinsky is applied as describing topoisomerase activated oligonucleotide adapters for covalently binding sequences. It is stated in

the Office Action that the skilled artisan would have been motivated to apply Yarovinsky's topoisomerase adapted vectors to the method of Shuman in order to bind amplified sequences into vectors.

As discussed above, however, the claimed invention is distinguishable from Shuman in providing a method for covalently linking both strands of at least one end of the first ds nucleotide sequence to both strands of at least one end of the second ds nucleotide sequence to generate a ds recombinant nucleic acid molecule that has no nick at the position of the joined ends. Yarovinsky does not describe a method of generating a ds recombinant nucleic acid molecule lacking a nick. Referring to Figure 1 (lower panel) of Yarovinsky, the topoisomerase activated adapter (lower panel, left) can be contacted with a target nucleic acid (exemplified as having a 3'dAMP overhang; lower panel, right), wherein the topoisomerase can covalently link the 3' terminus of the adapter to the 5' terminus of the target nucleic acid. As is evident, however, a nick will remain between the 5' terminus of the adapter (at the end containing the topoisomerase) and the 3' terminus of the target nucleic acid. As such, it is submitted that the claimed methods would not have been obvious over the cited references, whether considered alone or in combination, and, therefore, respectfully requested that the rejection of claims 6, 7, 11, 15 to 24, 27 and 35 as obvious over Shuman in view of Yarovinsky be removed.

The rejection of claims 42 and 43 under 35 U.S.C. § 103(a) as allegedly obvious over Shuman in view of Seed et al. is respectfully traversed.

Shuman is applied as discussed above. The Seed et al. reference is applied as describing a T7 suppressor gene in an expression vector. It is stated in the Office Action that one of ordinary skill in the art would have been motivated to apply Shuman's method of construction to express the T7 suppressor gene of Seed et al. in order to express and produce T7 suppressor, which can be used for diagnostic and therapeutic purposes.

As discussed above, however, the claimed invention is distinguishable from Shuman in providing a method for covalently linking both strands of at least one end of the first ds nucleotide sequence to both strands of at least one end of the second ds nucleotide sequence to generate a ds recombinant nucleic acid molecule that has no nick at the position of the joined ends. Seed et al. also do not describe a method of generating a ds recombinant nucleic acid molecule lacking a nick, according to the present invention. Instead, as stated in the Office Action, Seed et al. describe a T7 suppressor gene and expressing the T7 suppressor. As such, it is submitted that the claimed methods would not have been obvious over Shuman in view of Seed et al. and, therefore, is respectfully requested that the rejection of claims 42 and 43 as obvious over Shuman in view of Seed et al. be removed.

The rejection of claims 46 to 48 under 35 U.S.C. § 103(a) as allegedly obvious over Shuman in view of Trono et al. is respectfully traversed.

Shuman is applied as discussed above. The Trono et al. reference is applied as describing attaching a histidine tag to DNA. It is stated in the Office Action that one of ordinary skill in the art would have been motivated to apply the teaching of a histidine tag by Trono et al. to an expression system as described by Shuman in order to purify an expressed protein.

As discussed above, however, the claimed methods are distinguishable from Shuman in providing a method for covalently linking both strands of at least one end of the first ds nucleotide sequence to both strands of at least one end of the second ds nucleotide sequence to generate a ds recombinant nucleic acid molecule that has no nick at the position of the joined ends. Trono et al. also do not describe a method of generating a ds recombinant nucleic acid molecule lacking a nick, according to the present invention. Instead, as stated in the Office Action, Trono et al. describe a histidine tag and its use for purifying an expression product. As such, it is submitted that the claimed methods would not have been obvious over Shuman in

view of Trono et al. and, therefore, is respectfully requested that the rejection of claims 46 to 48 as obvious over Shuman in view of Trono et al. be removed.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Commissioner is authorized to charge Deposit Account No. 50-1355 if any fee is deemed necessary.

The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Respectfully submitted,

Date: June 28, 2004

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Enclosures: Replacement Figures 1A and 1B
Marked Versions of Original Figures 1A and 1B

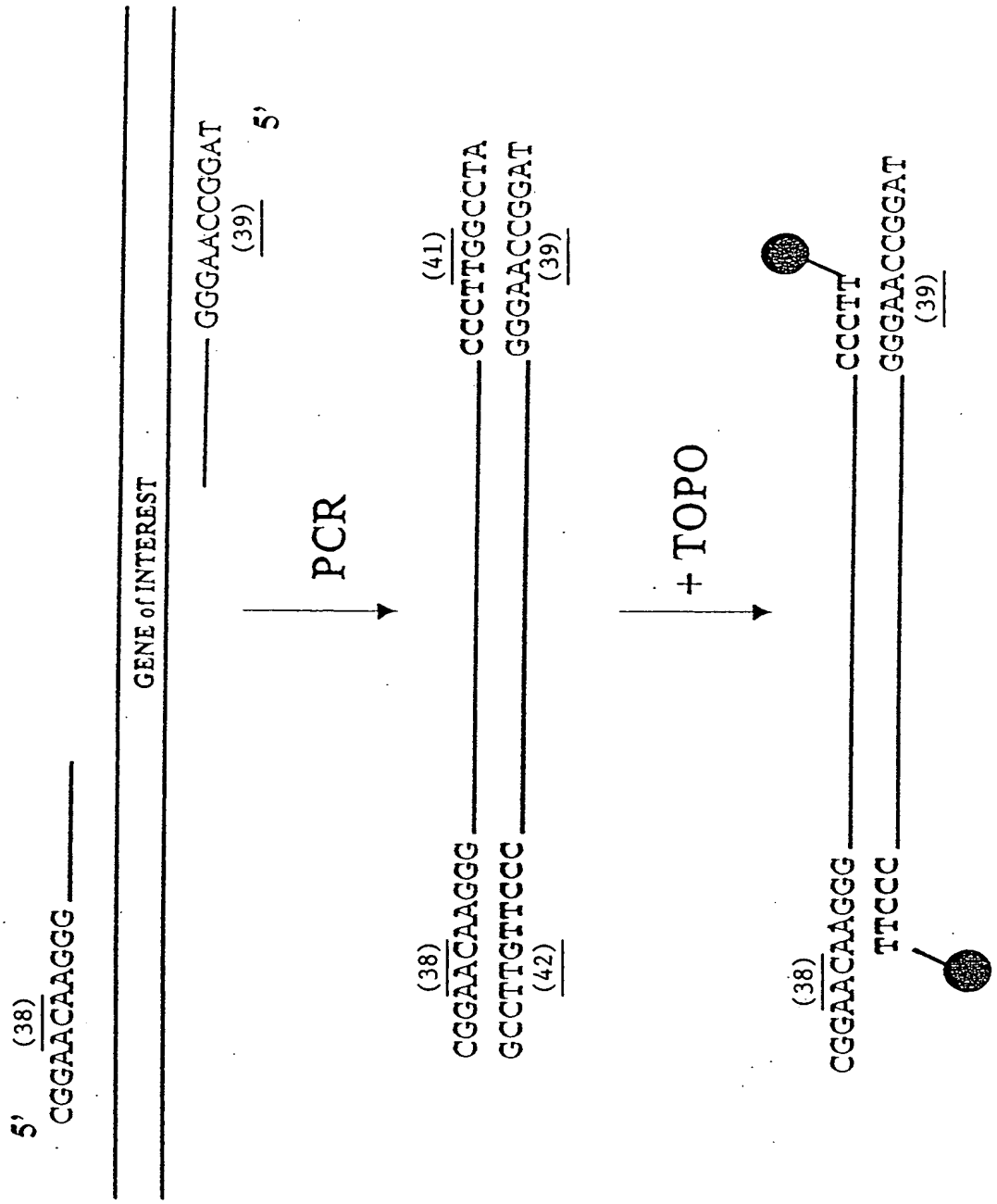

FIG. 1A

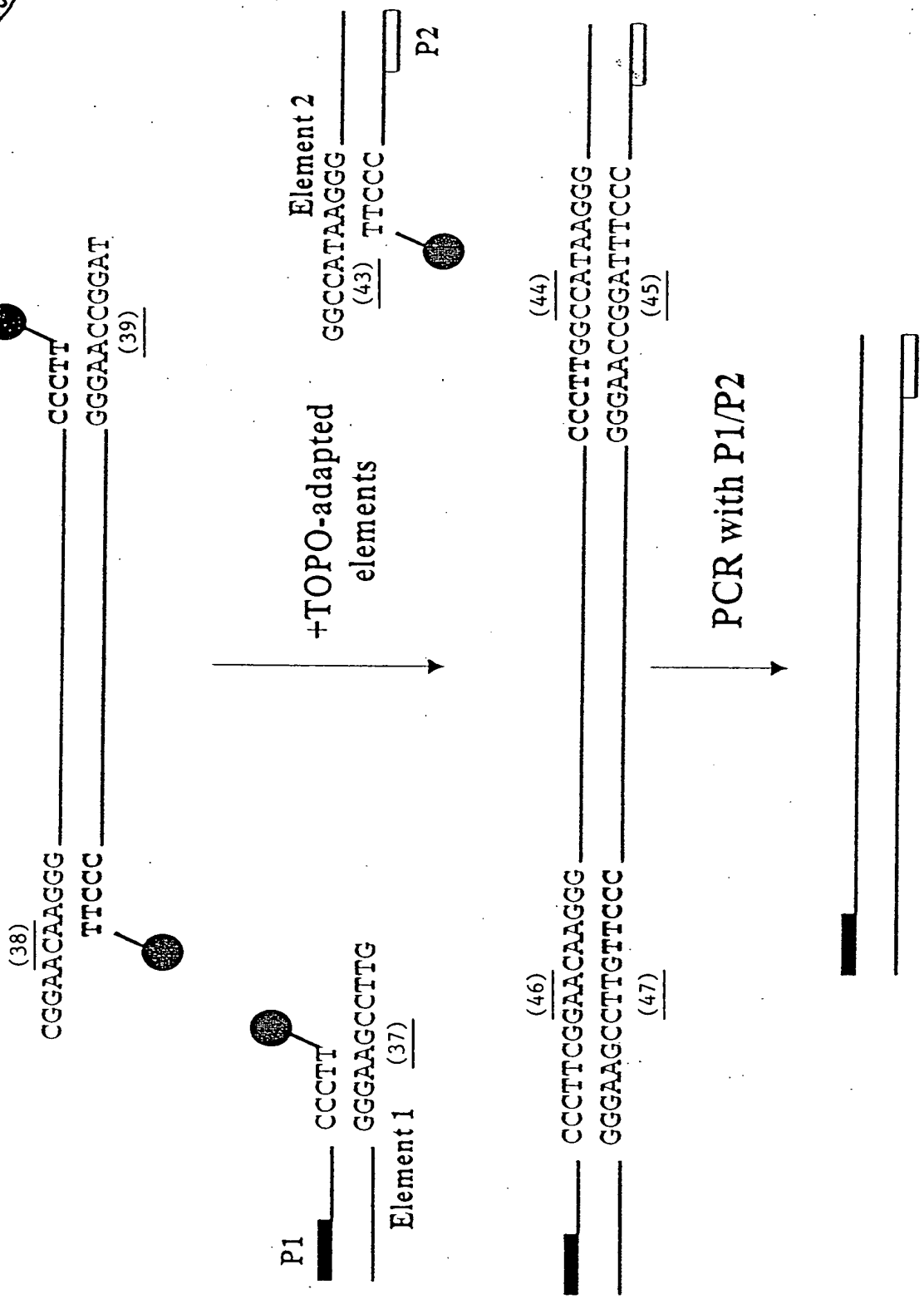

FIG. 1B